Exforge® (amlodipine and valsartan) Clinical Summary for Formulary Review

Please consult complete Prescribing Information

Exforge is a fixed-dose combination of the dihydropyridine calcium channel blocker (DHP CCB) amlodipine and the angiotensin II receptor blocker (ARB) valsartan. By complementary mechanisms, amlodipine and valsartan lower peripheral resistance, thereby lowering blood pressure. Amlodipine reduces calcium influx into vascular smooth muscle cells and valsartan reduces angiotensin II-induced vasoconstriction. Exforge is indicated for the treatment of hypertension. This fixed-dose combination is not indicated for the initial therapy of hypertension.

Antihypertensive Efficacy Compared With Amlodipine Alone and Valsartan Alone

In double-blind, placebo-controlled trials, blood pressure (BP) reductions were significantly greater with Exforge than with amlodipine alone and valsartan alone (Tables 1 & 2) (Exforge Prescribing Information).

Table 1. Mean change from baseline in SBP/DBP (mm Hg).

Placebo		Amlodipine 5 mg		Valsartan 160 mg		Valsartan 320 mg		Exforge 5/160 mg		Exforge 5/320 mg	
SBP	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**
–6.2	–6.4	–14.8*	–11.1*	–14.3*	–10.9*	–16.3*	–13.2*	–19.4†	–14.0†	–22.4†	–15.7†

**P* significant vs. placebo. †*P* significant vs. placebo, amlodipine, and valsartan.

Data from a double-blind, randomized trial (N=1911). Patients received placebo, amlodipine 2.5 mg or 5.0 mg, valsartan 40 mg-320 mg, or Exforge 5/160 mg or 5/320 mg for 8 weeks.

Table 2. Mean change from baseline in SBP/DBP (mm Hg).

Placebo		Amlodipine 10 mg		Valsartan 160 mg		Valsartan 320 mg		Exforge 10/160 mg		Exforge 10/320 mg	
SBP	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**
–11.0	–8.2	–22.2*	–15.0*	–18.1*	–12.8*	–18.5*	–12.8*	–26.6†	–17.2†	–26.9†	–18.1†

**P* significant vs. placebo. †*P* significant vs. placebo, amlodipine, and valsartan.

Data from a double-blind, randomized trial (N=1250). Patients received placebo, amlodipine 10 mg, valsartan 160 mg or 320 mg, or Exforge 10/160 mg or 10/320 mg for 8 weeks.

BP goals of <140/90 mm Hg and <130/80 mm Hg were achieved by 73% and 31% of patients treated with Exforge 10/320 mg, respectively (vs. 26% and 5% with placebo, respectively). BP control (<130/80 mm Hg) rates with Exforge 10/320 mg in patients with stage 1 hypertension, patients with stage 2 hypertension, and in elderly (≥65 yrs) hypertensive patients, were 49%, 20%, and 33%, respectively (vs. 6%, 3%, and 3% with placebo, respectively) (Philipp [poster], 2007).*

*BP <140/90 mm Hg and BP <130/80 mm Hg were not pre-specified endpoints. Stage 1 and stage 2 hypertension were not pre-specified subgroups.

Antihypertensive Efficacy in Patients Not Adequately Controlled With Amlodipine or Valsartan Monotherapy

In double-blind, active-controlled trials, BP reductions were significantly greater with Exforge than with amlodipine or valsartan monotherapy in hypertensive patients not adequately controlled with amlodipine or valsartan alone, respectively.

Table 3. Mean change from baseline in SBP/DBP (mm Hg).

Amlodipine 10 mg		Exforge 10/160 mg	
SBP	**DBP**	**SBP**	**DBP**
–10.8	–10.0	–12.7*	–11.8*

**P* significant vs. amlodipine.

Data from a double-blind, randomized trial (N=944). Patients who were not controlled after 4 weeks of treatment with amlodipine 10 mg were randomized to Exforge 10/160 mg or amlodipine 10 mg for 8 weeks.

Table 4. Mean change from baseline in SBP/DBP (mm Hg).

Valsartan 160 mg		Exforge 5/160 mg		Exforge 10/160 mg	
SBP	**DBP**	**SBP**	**DBP**	**SBP**	**DBP**
–8.2	–6.6	–12.0*	–9.6*	–13.9*	–11.4*

**P* significant vs. valsartan.

Data from a double-blind, randomized trial (N=947). Patients who were not controlled after 4 weeks of treatment with valsartan 160 mg were randomized to Exforge 5/160 mg, Exforge 10/160 mg, or valsartan 160 mg for 8 weeks.

Adverse Event Profile

Exforge has been evaluated for safety in over 2600 patients with hypertension; over 1440 of these patients were treated for at least 6 months and over 540 of these patients were treated for at least one year. Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall frequency of adverse experiences was neither dose-related nor related to gender, age, or race.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 2% of patients treated with Exforge but at a higher incidence in amlodipine/valsartan patients (n=1437) than placebo (n=337) included peripheral edema (5.4% vs. 3.0%), nasopharyngitis (4.3% vs. 1.8%), upper respiratory tract infection (2.9% vs 2.1%) and dizziness (2.1% vs 0.9%).

Dosage and Administration

In clinical trials with Exforge using amlodipine doses of 5 mg-10 mg and valsartan doses of 160 mg-320 mg, the antihypertensive effects increased with increasing doses.

A patient who experiences dose-limiting adverse reactions on either component alone may be switched to Exforge containing a lower dose of that component in combination with the other to achieve similar blood pressure reductions. Therapy with any combination of amlodipine and valsartan will be associated with both sets of dose-independent hazards.

A patient whose blood pressure is not adequately controlled with amlodipine (or another DHP CCB) alone or with valsartan (or another ARB) alone may be switched to combination therapy with Exforge.

For convenience, patients receiving amlodipine and valsartan from separate tablets may instead wish to receive tablets of Exforge containing the same component doses.

Important Considerations

USE IN PREGNANCY: When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Exforge (amlodipine and valsartan) should be discontinued as soon as possible. **See Warnings: Fetal/Neonatal Morbidity and Mortality**.

As with other drugs that work in the renin-angiotensin system, discontinue Exforge as soon as pregnancy is detected.

Exforge is contraindicated in patients who are hypersensitive to amlodipine or valsartan.

Excessive hypotension was seen in 0.4% of patients treated with Exforge. Volume and/or salt-depletion should be corrected in patients before administering Exforge or symptomatic hypotension may occur. Caution should be observed when initiating therapy in patients with heart failure or recent myocardial infarction and in patients undergoing surgery or dialysis.

Rarely, increased frequency, duration, and/or severity of angina or acute myocardial infarction have developed in patients treated with calcium channel blockers; particularly patients with severe obstructive coronary artery disease.

In patients with renal artery stenosis or severe renal impairment, care should be exercised with dosing of Exforge. In patients with severe HF, decline in renal function and rarely, acute renal failure and/or death has been associated with inhibiting the renin-angiotensin system.

Dosage reduction and/or discontinuation of the diuretic and/or valsartan may be required. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

Amlodipine is not a beta-blocker and therefore gives no protection against the dangers of abrupt beta-blocker withdrawal; any such withdrawal should be by gradual reduction of the dose of beta-blocker.

References

Exforge [Prescribing Information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; 2007.

Philipp T, Glazer R, Wersing M, et al. Dual calcium channel and angiotensin II receptor blockade is superior to amlodipine or valsartan alone for optimal hypertension control. Poster presented at The American Society of Hypertension, Inc. 22nd Annual Scientific Meeting and Exposition. Chicago, Illinois. May 19-May 22, 2007.

July 03, 2007.